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Review Article

Carbazoles and Tetrahydro carbazoles as Potential Therapeutic Agents- A Review on Its Chemistry, Synthesis and Biological Evaluation

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ABSTRACT

Carbazoles and their partially saturated analogues, tetrahydrocarbazoles, have attracted considerable interest in medicinal chemistry owing to their broad spectrum of pharmacological activities and structural versatility. These heteroaromatic compounds exhibit significant anticancer, antimicrobial, antiviral, anti-inflammatory, and neuroprotective properties. The rigid tricyclic core of carbazoles supports extensive chemical modifications, while tetrahydrocarbazoles provide enhanced molecular flexibility and metabolic stability, making them valuable scaffolds for therapeutic development. This review aims to summarize recent developments in the synthesis, chemical modifications, and biological applications of carbazoles and tetrahydro carbazoles, emphasizing their potential in drug discovery. Relevant literature was systematically analyzed to evaluate synthetic strategies for carbazole derivatives. Classical methods such as Fischer indole synthesis, Borsche-Drechsel method, and oxidative cyclization were reviewed alongside modern catalytic techniques. Structure-Activity Relationship (SAR) studies were also examined to understand the impact of substitution patterns on biological activity. Various synthetic approaches have enabled the preparation of structurally diverse carbazole derivatives with significant biological activities. SAR studies revealed that substitution at specific positions on the carbazole nucleus strongly influences pharmacological potency, selectivity, and therapeutic efficacy. Carbazoles and tetrahydro carbazoles remain promising scaffolds in medicinal chemistry. Continued advancements in synthetic methodologies and SAR-driven optimization may support the development of novel derivatives with improved pharmacological performance and clinical potential.

Keywords: Biological evaluation, Carbazoles, Synthesis, Tetrahydro Carbazoles, Therapeutic Agents.

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INTRODUCTION

Heterocyclic systems contain cyclic structures with several types of atomic species. The field of non-homocyclic chemistry plays a crucial role in drug discovery, as many such compounds exhibit significant medicinal properties. Among these, nitrogen containing heterocycles are particularly important.

Carbazole is one such compound, formed by the fusion of a central five membered ring with two benzene ring and the five membered ring connected with a nitrogen atom, which enables extensive electron delocalization. Carbazole and its derivatives represent an important class of aromatic heterocycles with excellent electron transporting and charge conducting abilities. Being nitrogen based aromatic systems, carbazole possess favourable electronic characteristics, a highly conjugated π system and a rigid structure that readily accommodates the introduction of various functional groups (Al Mohson *et al.*, 2021).

Moreover, the carbazolyl frame work allows for the incorporation of multiple substituents, leading to the development of novel derivatives. Due to these structural and electronic features, carbazole derivatives have found wide applications not only in chemistry such as dyes, photoactive materials and supramolecular recognition, but also in pharmacology. They display diverse biological activities, including antidiabetic, antitumour, anticonvulsant, antimicrobial, antioxidant, antifungal, antihistaminic, anti-inflammatory, antitubercular, antiviral,

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carbonic anhydrase inhibitory, neuroprotective and antidiarrheal effects.

In the biomedical field, carbazole derivatives are recognized for their notable anticancer properties. Their activity is mediated through several mechanisms, including insertion into DNA strands (DNA intercalation), suppression of topoisomerase activity, modulation of kinase signaling pathways and activation of apoptosis in malignant cells. They also demonstrate potent antimicrobial and antifungal properties, making them valuable in combating multidrug-resistant pathogens. Several carbazole analogues possess antiviral effects, including inhibition of HIV replication, suppression of hepatitis C virus activity, and activity against influenza strains. Their anti-inflammatory and antioxidative actions are connected to the downregulation of inflammatory mediators and the scavenging of free radicals, which is crucial in the management of chronic inflammatory and degenerative disorders. Carbazole derivatives have also been documented to possess anticonvulsant, antihistaminic, carbonic anhydrase inhibitory and neuroprotective properties, indicating their potential application in the management of epilepsy, allergic disorders, glaucoma and neurodegenerative conditions including Parkinson's and Alzheimer's.

1,2,3,4- Tetrahydrocarbazole is a partially saturated analogue in which the pyrrolic ring system is fused with an aromatic benzene ring and a saturated cyclohexane ring. This structural framework is commonly found in natural products and pharmacologically active compounds, underscoring its biological importance (Al Mohson *et al*., 2021). Derivatives of tetrahydrocarbazole have been reported to exhibit broad spectrum antimicrobial and antifungal activities, cytotoxic effects against various tumour cell lines, as well as notable analgesic and antinociceptive properties. In addition, these compounds demonstrate antidiabetic potential through enhancement of insulin sensitivity and modulation of glucose homeostasis along with antiobesitic effects via regulation of lipid metabolism. In the central nervous system, tetrahydrocarbazoles have demonstrated antipsychotic and antidepressant properties, in addition to antiemetic potential, which supports their use in neuropsychiatric disorders.

Carbazole and its 1,2,3,4-tetrahydro carbazole moieties are widely recognized for their diverse therapeutic actions, prompting continued research for novel physiologically significant derivatives. These scaffolds have been utilized in the development of antimicrobial agents, evaluated for antiproliferative effects in targeting tumour cells and evaluated for pain relieving, anti-obesity and type II antidiabetic effects. Moreover, they have shown potential in antipsychotic therapy and as antiemetic agents. Figure 1 shows the structure of carbazole and tetrahydrocarbazole (Figure 2).

This review will be of particular value to researchers in medicinal chemistry, pharmaceutical sciences, and organic synthesis, as it compiles and analyses the chemistry, synthetic strategies, and biological evaluation of carbazoles and tetrahydro carbazoles. The summarized structural activity relationships provide valuable guidance for drug discovery scientists in identifying potential lead compounds, while the comparative analysis of synthetic methodologies offers practical insights for organic chemists aiming at efficient scaffold construction. The review also serves as a resource for pharmacologists and biochemists, providing insights into the therapeutic potential of these heterocycles across various disease models. Furthermore, it can aid graduate students and academic instructors by offering a consolidated reference point for teaching and future research directions in heterocyclic and medicinal chemistry.

METHODOLOGY

A comprehensive literature search was conducted using databases such as PubMed, Google Scholar, ScienceDirect and Web of Science. Relevant peer-reviewed articles published in English were considered.

DISCUSSION

Chemistry of carbazole and tetrahydrocarbazole

Carbazole and tetrahydrocarbazole are both nitrogen-containing heterocycles with distinct chemical properties.

Carbazole

Carbazole ($C_{12}H_9N$), is a tricyclic ring system, with a pyrrole ring which is connected by two benzene rings. It is basic in nature due to the presence of nitrogen atom in the aromatic structure. The nucleus shows significant photochemical and electrochemical properties, which is useful in organic fields and as a dye. Carbazole shows electrophilic substitution reactions and nucleophilic reactions due to the nitrogen atom. Carbazoles found applications in organic semiconductors, Light-Emitting Diodes (LEDs), and in various pharmaceuticals (Aggarwal and Verma, 2019).

Tetrahydrocarbazole

Tetrahydrocarbazole ($C_{12}H_{13}N$), is a saturated derivative of carbazole, formed by the hydrogenation of the aromatic rings. This compound is highly flexible than carbazole towards the saturation of its rings. The partial saturation causes decrease in the electron density, and the compound is less reactive towards electrophiles when comparing with carbazole. It undergoes alkylation, acylation and ring opening reactions. It used as a solvent and as an intermediate in organic synthesis (Al Kaisy, 2010).

Both the compounds possess significant role in organic chemistry due to their structural and electronic characteristics.

Structural Activity Relationship of Carbazole and Tetrahydrocarbazole

The SAR of carbazole and tetrahydrocarbazole shows the importance of specific structural characteristics towards the reactivity and biological properties.

Carbazole

The stability of carbazole is due to its aromatic frame work and the π-π interactions are responsible for its biological properties.

The nitrogen atom in the carbazole is responsible for the basicity and chemical nature. This is responsible for the protonation and nucleophilic attack, which is important for the biological activities.

Modifications on the benzene or pyrrole ring can significantly alter biological activity. For instance, substitutions can enhance anticancer properties or change solubility and lipophilicity (Bailly, 2020).

The planar structure allows for efficient stacking interactions, which is beneficial in applications like organic photovoltaics.

Tetrahydrocarbazole

The decrease of aromatic character is due to saturation in the aromatic ring and this leads to change in chemical reactivity compared to carbazoles.

The saturated structure increases conformational flexibility, which can enhance its ability to fit into biological targets (e.g., receptors or enzymes).

The increased hydrophobic character can affect solubility and permeability, impacting bioavailability in drug design (Bhutani *et al.*, 2021).

Similar to carbazole, modifications to tetrahydrocarbazole can greatly influence its biological activity, including anti-inflammatory, analgesic, or antimicrobial properties.

In comparison, carbazole derivatives are often more potent in certain biological assays due to their aromaticity and ability to engage in π-stacking interactions, while tetrahydrocarbazole derivatives might be favoured for different types of biological activity due to their structural flexibility and saturation. Also, carbazole is more reactive towards electrophiles, while tetrahydro carbazole's reactions are often dominated by nucleophilic chemistry. Understanding the SAR of these compounds can inform the design of new derivatives with desired biological or chemical activities, guiding researchers in medicinal chemistry and material science (Caruso, 2023).

Synthetic Approaches to Carbazole and its Derivatives

Borsche- Drechsel Method for Carbazole Synthesis

Borsche- Drechsel Method for Carbazole Synthesis from 2-cyclohexylidene-1-phenyl hydrazine

From cyclization of 2- nitro biphenyls

Synthesis of carbazoles from cyclization of 2- nitro biphenyls

Oxidative dehydrogenation of 2- amino biphenyl

Oxidative dehydrogenation of 2- amino biphenyl for the synthesis of carbazoles.

Deamination of 2, 2'-diamino biphenyls

Deamination of 2, 2'-diamino biphenyls for the synthesis of carbazoles.

Synthesis of tetrahydrocarbazole and some derivatives

Boesche- Drechsel cyclization

Cyclohexanone phenyl hydrazone undergoes acid catalyzed rearrangement to yield tetrahydrocarbazole.

Fischer- Borsche cyclization for substituted 1,2,3,4-tetrahydrocarbazole

4- Methoxy phenyl hydrazine condenses with substituted cyclohexanones to form aryl hydrazones, which rearrange under acidic conditions (acetic acid/ HCl) to give substituted tetrahydrocarbazoles.

Thermal cyclization of the oxime of 2-phenyl cyclohexanone

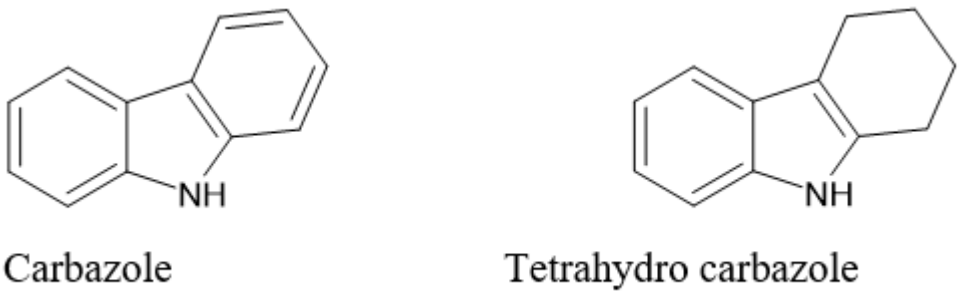


Figure 1: Structure of carbazole and tetrahydrocarbazole.

Oxime of 2-phenyl cyclohexanone on heating in aqueous ethanol forms 1,2,3,4-tetrahydrocarbazole.

Aqueous acid-mineral acid method

Phenyl hydrazine and cyclohexanone refluxed in presence of ethanol and hydrochloric acid yield 1,2,3,4-tetrahydrocarbazole.

Microwave Promoted Preparation of 1,2,3,4-tetrahydrocarbazole derivatives

Through microwave heating at 100 W and 140°C, 2-methoxy-4-nitrophenylhydrazine condenses with cyclohexanone in acetic acid to yield 6-nitro-8-methoxy-tetrahydrocarbazole.

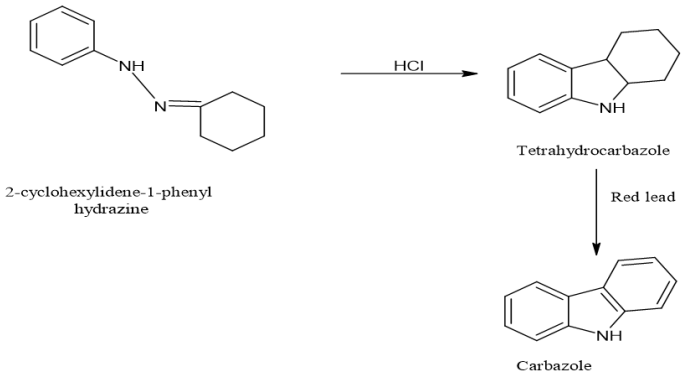
Synthesis of tetrahydrocarbazole using para-toluene sulfonic acid catalyst.

Phenyl hydrazine with cyclohexanone using para-toluene sulfonic acid catalyst at 90°C yield tetrahy drocarbazole.

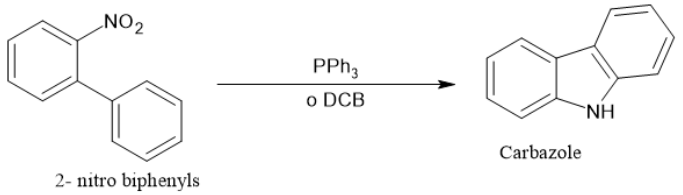
Following are the different schemes for the synthesis of carbazoles and tetrahydro carbazoles

Synthetic Schemes for Carbazole and its Derivatives

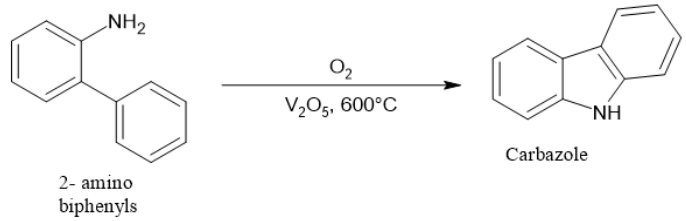
Borsche- Drechsel Method for Carbazole Synthesis



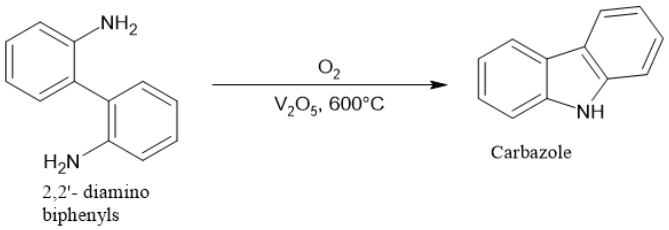
Synthesis from cyclization of 2- nitro biphenyls



Oxidative dehydrogenation of 2- amino biphenyl

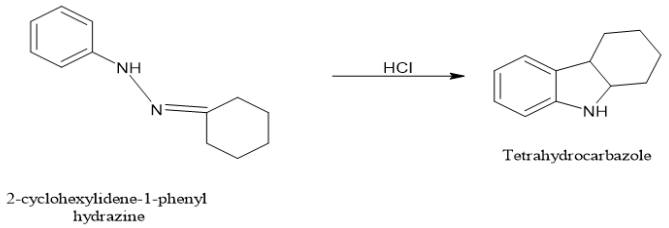


Deamination of 2, 2'-diamino biphenyls

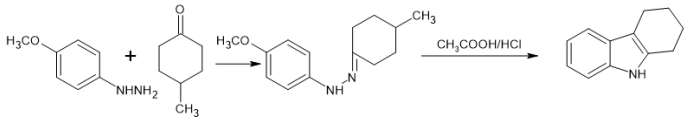


Synthesis of tetrahydrocarbazole and some derivatives

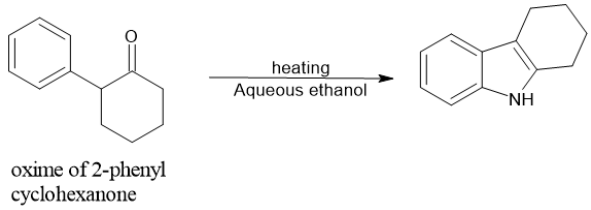
Boesche- Drechsel cyclization



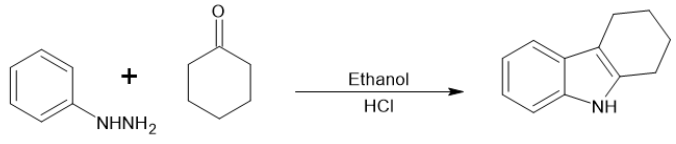
Fischer- Borsche cyclization for substituted 1,2,3,4-tetrahydrocarbazole



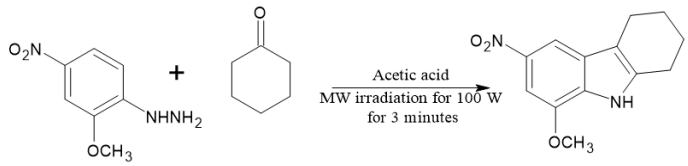
Thermal cyclization of the oxime of 2-phenyl cyclohexanone



Aqueous acid-mineral acid method



Microwave Promoted Preparation of 1,2,3,4-tetrahydrocarbazole derivatives



Synthesis of tetrahydro carbazole using para-toluene sulfonic acid catalyst.

Pharmacological Activity of carbazole derivatives

A study by *Gao et al. 2023* a set of carbazole moieties were formed to evaluate their cytotoxic property. The focus was on introducing

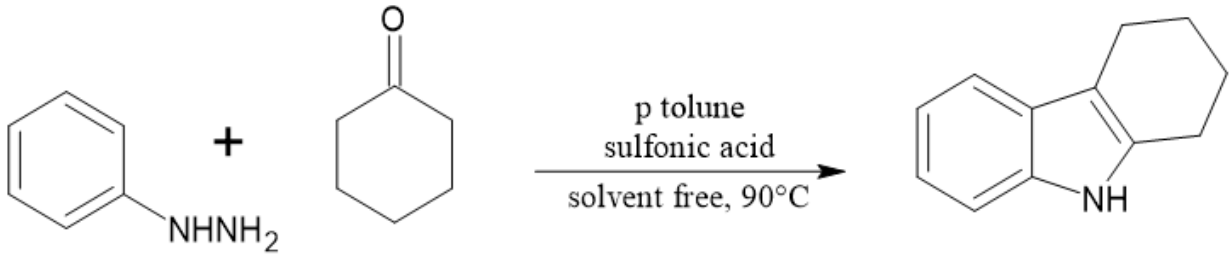


Figure 2: Different schemes for the synthesis of carbazole and tetrahydrocarbazole derivatives (Reactions 1-10).

structural diversity, comprising carbazole amides, hydrazides, and hydrazones, based on previously developed carbazole scaffolds.

The study focused on creating structural diversity by incorporating a methylene group, allowing for more rotatable bonds. The synthesized derivatives included various types of carbazole compounds, which were fully characterized using techniques such as ^{1}H and ^{13}C NMR, Electrospray Ionization-MS, HRMS and X-ray crystallography (Chakraborty and Panda, 2021; Chaudhary, 2016).

The cytotoxic potential of the synthesized compounds was assessed for adenocarcinoma, melanoma and African green monkey kidney (Vero) cells. Cell survival was assessed by the 3-(4,5- diMethyl Thiazol-2-yl)-2,5-diphenyl Tetrazolium bromide assay, revealing the inhibitory effects of the compounds. Notably, compound 14a exhibited pronounced cytotoxicity with IC_{50} values of 11.8±1.26 µM against gastric adenocarcinoma and 9.77±8.32 µM against human melanoma. The values indicate, the compound 14a Figure 3 may act as a lead compound for the formation of new carbazole based antitumour derivatives. Table 1. Shows the IC_{50} values of Compound 14a.

The anticancer activity was assessed by SPSS software. This study points out the cytotoxic effects of various carbazole derivatives (El-Nassan, 2015).

In a study, *Zhontang et al. 2023* developed novel carbazole and tetrahydro carboline derivatives for binding with dopamine D_3 receptor (D_3R), enhancing the antipsychotic activity. The work was intended to achieve enhanced selectivity of D_3 receptor over D_2 receptor to enhance the potential activity and to minimise adverse effects. Among the compounds identified, ZLG-25 Figure 3 developed as a bifunctional ligand, with a binding affinity of 685 nmol/L for D_3 receptor and >10000 nmol/L for D_2 receptor.

Using a structure based computational methods, they developed a series of analogues containing tetrahydro-β-carboline and tetrahydro-γ-carboline nucleus. Many of the moieties possess selective antagonists at D_3R. The compounds 23j and 36b has better responses. Particularly, compound 36b demonstrated antidepressant like activity in behavioural assays, including the Forced Swing Test (FST) and Tail Suspension Test (TST).

Preliminary evaluations indicated that compound 36b possessed a favourable safety profile, showing no weight gain and minimal serum prolactin evaluation- common side effects associated with antipsychotic therapies. Here derivative 36b as a lead derivative for future investigation, with potential applications in the treatment of psychotic disorders.

Overall, this study underscores the value of carbazole and tetrahydro carboline scaffolds in the design of selective D_3R antagonists and highlights compound 36b as a strong candidate for future clinical exploration in antipsychotic drug development.

Irfan Capan et al. 2023 developed and synthesized a new set of carbazole derivatives with an emphasis on their anticancer and antioxidant potential. The research sought to design novel carbazole scaffolds and assess their antiproliferative and antioxidant activities. A total of eight derivatives were obtained and structurally confirmed using HRMS and NMR analysis. Their anticancer, antifibrotic and antioxidant effects were systematically evaluated through standard biomedical assays. Additionally, molecular docking studies with Auto Dock Vina were conducted to explore their binding interactions with biological targets.

Compounds 10 and 11 demonstrated significant antiproliferative effects against HepG2 (liver cancer), HeLa (cervical cancer), and MCF7 (breast cancer) cells, with half maximal inhibitory concentration values of 7.68, 10.09, and 6.44 µM respectively. Derivative 9 also possessed strong action against HeLa cells with a half maximal inhibitory concentration of 7.59 µM. Medium potential was found against Caco-2 (colorectal tumour) cell lines, with half maximal inhibitory concentration from 43.7 - 187.23 µM

Compound 9 was identified as the most potent antifibrotic agent, showing 57.96% cellular viability at a 1 µM concentration compared to the positive standard, 5-Fluorouracil.

Compounds 4 and 9 exhibited strong anti-oxidant properties, with half maximal inhibitory concentration range of 1.05 and 5.15 µM, respectively Figure 3 shows the structures of Compound 4,9,10,11.

The computational docking analysis revealed that derivative 3 had the highest docking score (-11.3 kcal/mol) against the XDH binding site, while compound 11 showed high affinity (- 11.1 kcal/mol) for the PPARG active site. The docking results were corroborated by CB-Dock analyses, confirming the binding interactions.

All synthesized compounds complied with Lipinski's draggability properties, denotes their likelihood of oral absorption. Mainly, derivatives 10 and 11 were exhibited to penetrate the Blood-Brain Barrier (BBB) (Eseyn *et al*., 2018).

The novel carbazole compounds shows better antiproliferative, antioxidant and antifibrotic effects. Also *in vivo* studies support the development of new anticancer drug molecules.

In a study by *Fang et al. 2021* used Diels Alder reaction for the synthesis of carbazole and pyrrolo 3,4-c carbazole derivatives. Here occurs the use of p-TsOH catalyzed Diels Alder reaction between 3-(indol-3-yl) maleimides and chalcones in toluene at 60°C, forms two diastereo isomeric forms of tetrahydro pyrrolo 3,4-c carbazoles. These intermediates undergo aromatization reaction with DDQ oxidation in acetonitrile at room temperature, yielding pyrrolo 3,4-c carbazoles derivatives.

A new synthesis of carbazoles was also developed in presence of p-TsOH and DDQ by reacting 3-(indol-3-yl)-1,3-diphenyl propan-1-ones with chalcones or benzylidene acetone in acetonitrile. The above reaction mechanism includes oxidative dehydrogenation, Diels Alder cycloaddition and aromatization.

The main advantage of this method is fast availability of raw materials high efficiency with atom economy. On conclusion the above study represents an efficient method for the synthesis of polyfunctionalized carbazole derivatives using Diels Alder Reaction and the method is a new milestone in future drug development (Fang *et al*., 2021).

In a study by *Eseyin et al. 2018* a series of alkyl analogues of carbazole were prepared and tested for *in vitro* antidiabetic effects, specifically focusing on their inhibition on alpha-amylase and alpha-glucosidase enzymes.

Acid catalyzed alkylation method was developed to prepare methyl, ethyl propyl and butyl carbazole derivatives.

In *in vitro* Antidiabetic Activity, the Enzyme Inhibition Assays are alpha amylase inhibition and alpha glucosidase inhibition. In case of α-Amylase Inhibition, the half maximal inhibitory concentration values for the synthesized derivatives were identified as follows: Carbazole: 87.47 µg/mL, Methyl carbazole: 50.23 µg/mL, Ethyl carbazole: 47.20 µg/mL, Propyl carbazole: 42.36 µg/mL, Butyl carbazole: 42.11 µg/mL. In α-Glucosidase Inhibition**,** only ethyl carbazole, propyl carbazole, and butyl carbazole showed significant activity with IC_{50} values of 205.30, 153.93, and 152.90 µg/mL respectively. Carbazole and methyl carbazole exhibited null antagonistic potential on α-glucosidase. Table 2. shows the IC_{50} values of Carbazole Derivatives

This study concluded that the alkylation of carbazole increased ability to inhibit α-amylase, with activity correlating positively with the alkyl chain length. While none of the synthesized derivatives surpassed the reference compound (acarbose) in inhibitory activity, the findings suggest that alkyl-carbazole derivatives could be promising leads for the formation of new antidiabetic compounds.

In Alpha-Amylase Assay, the inhibitory effect was measured using a standard procedure involving sodium phosphate buffer and dinitro salicylic acid, with absorbance read at 540 nm and in Alpha-Glucosidase Assay**,** utilized p-nitrophenyl-alpha-D-glucopyranoside as a starting compound, with absorbance measured at 410 nm (Eseyin *et al*., 2018).

The research supports the potential of alkyl-carbazole compounds as candidates for further investigation in the search for effective α-amylase inhibitors, highlighting their potential utility in managing diabetes.

In the study by *Liu et al. 2015* a collection of new N-substituted carbazole based imidazolium salts were prepared and analyzed for their anticancer property towards various mammalian tumor cells.

A total of 57 N-substituted carbazole imidazolium salts (compounds 5-61) were prepared and tested. Cytotoxicity was assessed towards 5 mammalian tumor cells: HL-60 (myeloid leukemia)**,** SMMC-7721 (liver cancer)**,** A549 (lung cancer)**,** MCF-7 (breast adenocarcinoma)**,** SW480 (colon cancer).

Compounds exhibited varying levels of cytotoxicity, with some showing significant activity (IC_{50} values) against the tested cell lines. Carbazole and imidazole controls showed no activity at 40 µM, while the newly synthesized derivatives demonstrated moderate to good cytotoxic potential. Compound 61 featured a 2-bromobenzyl substituent and exhibited activity with half maximal inhibitory concentration values ranging from 0.51 and 2.48 µM across multiple cultured cells. Also, Compound 22 with a naphthyl acyl substituent, displayed stronger cytotoxic activity with IC_{50} values ranging from 2.69-5.65 µM. Table 3. Shows the IC_{50} values of Compound 61 and 22.

Structure-Activity Relationship (SAR) influence of Substituents, impact of alkyl chains, effect of imidazole ring type etc. in case of influence of substituents, compounds with the 5,6-dimethyl-benzimidazole moiety and specific substituents at the imidazolyl-3-position (e.g., 2-bromobenzyl or naphthyl acyl) exhibited stronger anticancer property. The alkyl chain length connecting the carbazole scaffold to the imidazole moiety positively correlated with increased cytotoxicity (n=3>2>1). In case of Alkyl Chains, the Propyl derivatives (14-28) showed relatively weak activities, Butyl derivatives (29-46) shows medium anticancer properties with half maximal inhibitory concentration

Table 1: IC_{50} values of Compound 14a.

Derivative	Cell Line	IC_{50} (µM)
Compound 14a	Gastric adeno carcinoma	11.8±1.26
Compound 14a	Human melanoma	9.77±8.32

Table 2: IC_{50} values of Carbazole Derivatives.

Derivatives	Enzyme	IC_{50} (µg/mL)
Carbazole	α- Amylase	87.47
Methyl carbazole	α- Amylase	50.23
Ethyl carbazole	α- Amylase	47.20
Propyl carbazole	α- Amylase	42.36
Butyl carbazole	α- Amylase	42.11
Ethyl carbazole	α- Glucosidase	205.30
Propyl carbazole	α- Glucosidase	153.93
Butyl carbazole	α- Glucosidase	152.90

values from 0.49 to 19.98 µM and pentyl derivatives (47-61) showed more cytotoxic properties with IC_{50} range less than 4.50 µM). The Effect of Imidazole Ring Type ie, compounds with the imidazole ring showed lower activities compared to those with benzimidazole or 5,6-dimethyl substituted benzimidazole moieties. The most potent derivatives were those containing the 5,6-dimethyl substituted benzimidazole compound.

The action includes programmed apoptosis and blockade of cell cycle development. Compound 61 shows cell cycle inhibition and programmed apoptosis in SMMC-7721 liver cancer cells, shows potent anticancer effects (Kobayashi and Kuzuyama, 2020).

They point out the N-substituted carbazole imidazolium salts act as better lead for anticancer drug development. Figure 3 shows 5,6 dimethyl benzimidazole substituted carbazole. The structure-activity relationships provide instructions for improving the therapeutic activity.

Mustafa et al. 2022 synthesized tetrahydrocarbazole derivatives by reacting cyclohexanone with phenyl hydrazine, yielding Tetrahydro Carbazole (THCZ). These derivatives were rearranged by generating amide linkage with ketoprofen, indomethacin and diclofenac like NSAIDs. *In vitro* analysis and molecular docking studies reveals the antimicrobial activity against both gram positive and gram-negative organisms. Ciprofloxacin and fluconazole are the standard drugs used for comparison. Maximum activities are shown by the compounds CD and CI, Figure 3 (Kumar and Chowdhary, 2022; Lanka *et al.*, 2015).

Zahraa et al. 2021 encompasses the condensation and Schiff base methods for synthesizing new N- substituted tetrahydro carbazole derivatives. The compounds were characterized using spectral methods and evaluated for antioxidant activity compared to ascorbic acid. Another study by Zahraa *et al.* detailed the preparation of new pyrazole compounds from cyclohexanone along with their subsequent reactions. Antimicrobial activities were tested against multiple bacterial and fungal strains using a well diffusion method. Notably, certain compounds showed maximum blockade towards *E. coli, K. pneumoniae*, and *S. aureus*, with amoxicillin and ciprofloxacin serving as standards for comparison.

In a study, *Wang et al. 2021* focused on the development, synthesis along with evaluation of tetrahydrocarbazole derivatives, building upon the promising candidate ZG02. They created two series of these derivatives and screened them for assessing glucose metabolism in HepG2 cell models.

From the various derivatives, compound 12b ie, an aza tetrahydro carbazole compound shows more hypoglycemic effect. This leads to 45% increase in glucose absorption while comparing with standard drug. This result is 1.2 times more than that of standard drugs.

This study emphasizes the development of new antidiabetic agents with the help of tetrahydrocarbazole derivatives Figure 3 shows compound 12b.

In a study, *Vijayalekshmi et al. 2019* addressed the growing issue of drug resistance, highlighting the urgent need for novel compounds to combat this challenge. Carbazole derivatives, particularly 1,2,3,4-tetrahydrocarbazole are recognized for their diverse biological activities, driving interest in developing new derivatives with enhanced antimicrobial efficacy.

The antimicrobial evaluation involved both antibacterial and antifungal assays. For antibacterial activity, the cup plate method was used, where antibiotics diffuse through agar to inhibit microbial growth, forming a clear zone around the cup. Similarly, agar diffusion method was used to monitor antifungal activity.

Among the tested compounds, TCZ-1b and TCZ-2a demonstrated strong potential towards Gram positive and Gram-negative organism. TCZ-1a and TCZ-2b showed moderate antibacterial activity with TCZ-1a particularly effective against *E. coli.* Figure 3 shows the structure of Compound TCZ-1b and TCZ-2a. The derivative TCZ-1d shows antifungal potential. While comparing with the standard drugs streptomycin and miconazole nitrate, the derivatives TCZ-1, TCZ-1a and TCZ-2b shows medium activity while others possess no activity.

This study mentions the development of novel antimicrobial agents from tetrahydrocarbazole derivatives.

By using brominated derivatives of tetrahy drocarbazole, *M Sathiya, 2018* reported some novel antibacterial agents. Electrophilic bromination and free radical bromination are the two different strategies used for the synthesis. Compound A (2,7-dibromo-1,2,3,4- tetrahydro carbazole) was prepared using N-bromosuccinimide and concentrated sulphuric acid by electrophilic bromination method. Also, by free radical bromination Compound B (2,6-dibromo-1,2,3,4-tetrahydro carbazole) was prepared.

By using Fourier Transform Infrared Spectroscopy (FTIR), Proton Nuclear Magnetic Resonance (^{1}H NMR), carbon-13 Nuclear Magnetic Resonance (^{13}C NMR) and Mass Spectrometry (MS) characterization is done. Agar well diffusion method was

used for antibacterial evaluation. The standard drug used for the comparison is ciprofloxacin.

The study mainly emphasizes the future development of new antibacterial derivatives by bromination methods.

Zhang et al. 2018 designed a set of tetrahydro carbazole derivative and prepared as potential activators of AMP-Activated Protein Kinase (AMPK), focusing on their hypoglycemic and hypolipemic effects.

The glucose absorption in HepG2 liver tumour cells for the novel compounds was analyzed. Compound 7a, featuring a para-chloro-benzoyl substituent, demonstrated the highest glucose consumption increase of 82.5%, surpassing the control group (DMSO) and exhibiting activity comparable to the standard drug pioglitazone.

Various substituents on the C-6 position generally showed weaker activity, likely due to steric hindrance affecting interactions with AMPK. Substituents on the nitrogen atom of the tetrahydrocarbazole scaffold also influenced activity, with electron-withdrawing groups enhancing hypoglycemic effects.

Compounds 7a and 8b were undergo *in vivo* assessment in diabetic mice. Both compounds significantly reduced blood glucose levels, with 7a achieving a reduction of 30.6% compared to the positive control group after oral administration. After three weeks, 7a showed sustained hypoglycemic effects, while exhibiting a lower impact on body weight compared to other treatments.

The pharmacokinetic profiles of 7a, Figure 3 were evaluated, supporting its potential for further development.

The study highlights the promise of tetrahydrocarbazole derivatives, particularly compound 7a, as effective AMPK activators with significant hypoglycemic and hypolipemic effects. The findings suggest these compounds could serve as a foundation for developing new therapeutic agents for managing diabetes, with ongoing structure-activity relationship studies aimed at optimizing their efficacy.

In the study *Sadiq et al. 2017* a new set of tetrahydro carbazole linked 1,2-diazoles (designated as compounds a-o) were synthesized using a microwave-assisted multicomponent reaction approach.

Microwave-Assisted synthesis involved a Michael addition of hydrazines α, β-unsaturated ketones generated *in situ*, which were produced through an aldol-type strategy. The best yields were obtained by using equal amounts of water and acetic acid under microwave irradiation, completing the reaction in just 4 min.

The synthesized compounds were achieved in medium to higher yields, showcasing the efficiency of microwave-assisted technique. The study encourages the use of microwave assisted derivatives in developing novel tetrahydro carbazole linked 1,2-diazoles and the compounds can be developed as valuable potential in the field of medicinal chemistry.

Padmavathi et al. 2016 mentioned substituted tetrahydrocarbazole derivatives as antimicrobial agents. Condensation reaction of substituted phenyl hydrazines with cyclohexanone was used for the synthesis of derivatives. From these intermediates, N-substituted tetrahydro carbazole derivatives were formed by the reaction of substituted aromatic acid chlorides in alkaline media. The formed compounds were characterised by IR, NMR and mass spectroscopic analysis.

The antimicrobial activity was assessed using the agar cup plate technique against bacterial flora (*Staphylococcus aureus, Escherichia coli, Bacillus subtilis, Pseudomonas aeruginosa*) and fungal flora (*Candida albicans, Aspergillus niger*). Eight compounds exhibited significant antimicrobial effects with pronounced zones of inhibition, attributed to the nature of the substituents on the tetrahydrocarbazole scaffold.

Overall, the study demonstrates that the synthesized tetrahydrocarbazole derivatives, shown in Figure 3 possess promising antimicrobial activity and effective inhibition of GlcN-6-P synthase, supporting their further development as potential antimicrobial agents. This work underscores the versatility and medicinal potential of tetrahydrocarbazole derivatives in drug discovery, particularly for antimicrobial applications.

Chaudhary et al. 2016 prepared a group of 2,3,4,9-tetrahydro-1H-carbazole analogues and evaluated their anticancer activity against the A-549 lung cancer cell lines. Compound J3 (p-bromo acetophenone) and J4 (p-nitro acetophenone) showed significant cytotoxicity, while other derivatives were largely inactive. This study highlights tetrahydrocarbazole derivatives as promising scaffolds for anticancer drug development and warrants further exploration of their therapeutic potential Figure 3 shows the substituted derivative.

Lanka et al. 2015 reported the development of a set of N- substituted tetrahydrocarbazoles and evaluate their anticonvulsant property, along with other pharmacological properties. The synthesis involved reacting cyclohexanones with substituted hydrazine hydrochlorides in glacial acetic acid to yield N-(1,2,3,4-tetrahydro carbazole) intermediates, which were further elaborated into derivatives containing various heterocycles, including sulfur and nitrogen containing rings.

Table 3: IC_{50} values of Compound 61 and 22.

Derivatives	IC_{50} (μM)
Compound 61	0.51-2.48
Compound 22	2.63-5.65

All the prepared compounds were achieved using infrared spectroscopy, proton NMR and carbon-13 NMR spectroscopy. The derivatives were assessed for analgesic, anti-inflammatory and anti-convulsant activities.

This study demonstrates the therapeutic potential of tetrahydrocarbazoles and their derivatives as pharmacologically valuable compounds and emphasized the importance of developing new heterocyclic derivatives to enhance their biological applications Figure 3 shows the Substituted N-(4-amino benzoyl) 1,2,3,4- tetrahydro carbazole derivatives.

An investigation by *Surendiran, 2015* the anti-inflammatory potential of isoxazolinyl, pyrazolinyl and chalconyl derivatives of 1,2,3,4-tetrahydrocarbazoles was evaluated.

The derivatives of isooxazoline and pyrazoline were synthesized by reacting chalconyl-1,2,3,4-tetrahydro carbazoles with hydroxyl amine hydrate and hydrazine hydrate respectively.

Their inflammation inhibiting effect was tested by the carrageenan mediated paw oedema method in male Wistar rats. In this method, inflammation was produced by injecting 1% carrageenan suspension into the ventral surface of foot region of the rats left rear paw and foot swelling was monitored at different intervals with help of a mercury displacement plethysmograph.

Before the carrageenan challenge, the animals were treated with the synthesized carbazole derivatives or with the vehicle control (DMF). Paw volume measurements were taken at intervals (30, 60, 90, 120, 180, and 240 min) post-injection to calculate the percentage inhibition of inflammation.

Figure 3. shows the Structure of Chalconyl and Pyrazolinyl derivatives. Majority of the synthesized derivatives exhibited significant anti-inflammatory activity, demonstrating their potential therapeutic efficacy. The study highlighted the effectiveness of various tetrahydrocarbazole derivatives in reducing inflammation, suggesting their potential as novel anti-inflammatory agents. This research contributes to the ongoing exploration of tetrahydrocarbazole derivatives in medicinal chemistry, particularly for their anti-inflammatory properties.

In a study by *Parthiban et al. 2014* a set of modified tetrahydrocarbazole derivatives were prepared and analyzed for their bacterial and fungal inhibitory effects.

The study focused on N-((5,6,7,8-tetrahydrocarbazol-9-yl) methyl) amine derivatives (PM1-PM5). These compounds were prepared and characterized for their possible biological activities.

The prepared derivatives were tested against various bacteria: *Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumonia, Salmonella typhii*, and *Staphylococcus aureus*. Amoxicillin served as the standard for comparison. Notably, compound PM1 showed moderate potential against *S. aureus* and showed effectiveness towards all tested bacterial strains. Compound PM5 was observed to be inactive against gram-positive bacteria.

The antifungal activity was tested against *C. albicans* and *Aspergillus niger* at doses of 50 and 100 µg/mL, with griseofulvin as the standard. Compounds PM1 and PM3 demonstrated better antifungal activity at 100 µg/mL, while all compounds showed no antifungal activity at 50 µg/mL.

The structure-activity relationship suggested that compound PM1, Figure 3 has promising potential as a prototype molecule for the discovery of novel antimicrobial compounds, given its efficacy against multiple bacterial strains. This research underscores the therapeutic potential of tetrahydrocarbazole derivatives in combating infections, paving the way for further development in antimicrobial research.

In a study by *El-Nassan, 2014* a series of tetrahydrocarbazole derivatives hybridized with dithioate compounds were prepared and analyzed for their antitumor effect.

Three series of compounds were prepared: Alkyl dithiocarbonates, Heterocyclic dithio carbamates, Di alkyl dithio carbamate. These compounds were designed to analyze the rate of different alkyl derivatives on antitumor activity.

The new derivatives were evaluated *in vitro* on adenocarcinoma cell line (MCF7) and colon cancer cell line (HCT116) using the Sulforhodamine-B (SRB) assay. Among the compounds, 6f, Figure 3, (a 4-chlorophenylpiperazine derivative) demonstrated potent cytotoxicity towards the breast carcinoma cell line, surpassing the activity of doxorubicin with an half maximal inhibitory concentration range of 7.24 nmol/L.

The study indicated that MCF7 cells were highly sensitive to the new derivatives than HCT116 cells. The SAR analysis revealed that: Heterocyclic dithio carbamates (particularly those with piperazine) were more effective than dialkyl dithiocarbamate (7) against MCF7 Alkyl dithiocarbonates exhibited greater anticancer potential than heterocyclic compound dithiocarbamates derived from piperidine or morpholine rings. In terms of piperazine derivatives, the order of potency was found to be 4-chloro phenyl > alkyl > 4-methoxy phenyl > phenyl.

The study successfully synthesized novel tetrahydrocarbazole-dithioate hybrids with significant antitumor activity. More studies are required to know the impact of the linker between tetrahydrocarbazole and dithioate, as well as to elucidate the mechanisms behind the observed antitumor effects. This research highlights the potential of tetrahydrocarbazole derivatives in cancer treatment and lays the groundwork for further studies on their therapeutic applications.

In a study by *Harsha et al. 2012* a set of new tetrahydrocarbazole compounds were prepared and analyzed for their potential anticancer activities.

Tetrahydrocarbazole was synthesized via Fischer indolization, reacting cyclohexanone with phenyl hydrazine in acetic acid. Cycloaddition of tetrahydrocarbazole with various substituted aromatic aldehydes produced a range of tetrahydrocarbazole derivatives (A1-A10). The tetrahydrocarbazole derivatives were prepared under optimal conditions using concentrated sulfuric acid as a promotor and ethanol as the dissolving medium achieving high yield of target molecules. Structural confirmation was performed through IR spectroscopy, ^{1}H NMR and mass spectrometry.

The derivatives, shown in Figure 3 were then assessed for *in vitro* anticancer efficacy against HT-29 (colon cancer) cell cultures. Cell damaging was determined using the MTT assay, which measures the reduction of MTT to a coloured product with absorbance recorded at 492 nm. IC_{50} values were calculated from the percentage inhibition of cell proliferation. Notably, several derivatives-A3, A4, A5, A7 and A9 demonstrated significant cytotoxic effects on HT29 cells, suggesting strong anticancer potential.

Overall, this study underscores the synthesis and biological evaluation of tetrahydrocarbazole derivatives, highlighting their promising anticancer properties. These molecules may serve as lead candidates for further optimization and development in cancer therapy.

Wafa a Al-Kaisy, 2010 reported the formation of a series of novel 1,2,3,4- tetrahydro carbazole derivatives incorporating thiazole and 1,2,4-triazole moieties and their biological activities were subsequently assessed.

The synthetic route commenced with the reaction of tetrahydrocarbazoles with ethyl chloro acetate in presence of potassium hydroxide using a fusion method, resulting in the formation of 1-(ethyl acetate)-1,2,3,4-tetrahydro-9H- carbazole. This ester was then converted to various derivatives, including semicarbazides, thiosemicarbazides, urea, and thiourea. Cyclization of these derivatives in alkaline media led to the formation of substituted triazoles. Further reactions with p-bromophenyl bromide resulted in the synthesis of oxazole and thiazole derivatives. Hydrazine treatment of the ester produced a hydrazine derivative, which was cyclized to give more substituted triazoles.

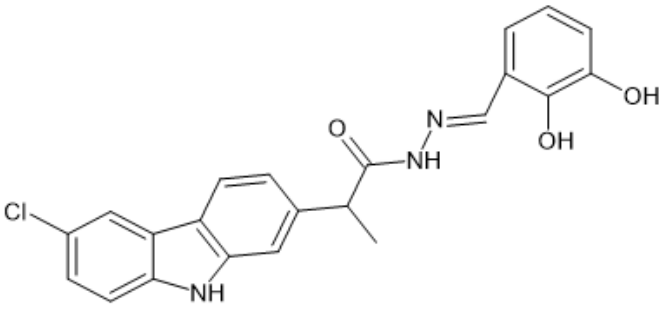
The prepared derivatives were analyzed using FTIR, proton and carbon 13 -NMR spectroscopy, along with physical property measurements.

Antimicrobial activities were tested against various bacterial strains: *Staphylococcus aureus, Staphylococcus epidermidis, Pseudomonas aeruginosa,* and *Escherichia coli*, as well as one yeast strain (*Candida*). The disk diffusion method was employed, with sterile paper disks impregnated with the compounds and incubated to observe inhibition zones.

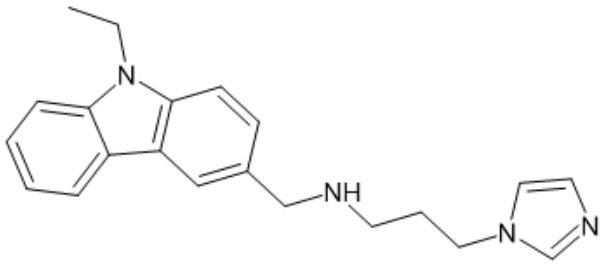
All derivatives showed medium to vast activity against *Candida*. Compound 12 exhibited more potential towards one bacterial strain, while compounds 2, 7, 12, and 15 demonstrated moderate activity against two types of bacteria. Compounds 6, 7, and 15 displayed high activity against specific bacterial strains, whereas compounds 2, 6, 11, and 13 showed inactivity against two bacterial types.

This study successfully synthesized novel tetrahydrocarbazole derivatives with potential antimicrobial properties. The findings indicate that certain compounds, particularly compound 12, Figure 3, possess significant antibacterial activity, suggesting their potential as leads for further development in antimicrobial research.

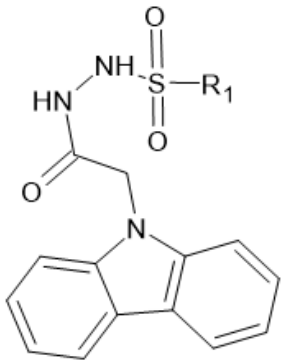
Structures of Specific Compounds



Compound 14a

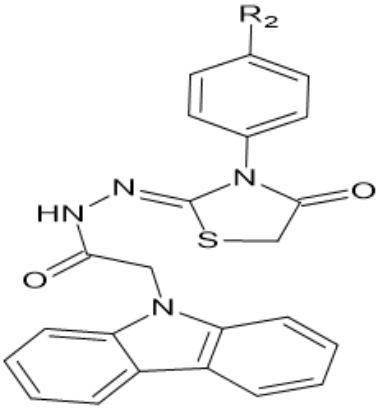


ZLG 25



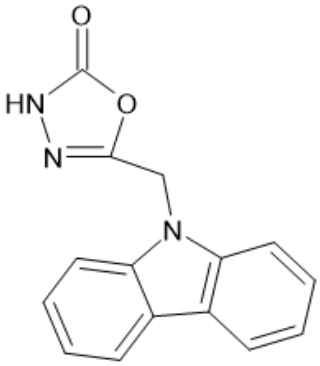
Compound 4

R_1=p-OCH_3-Ph

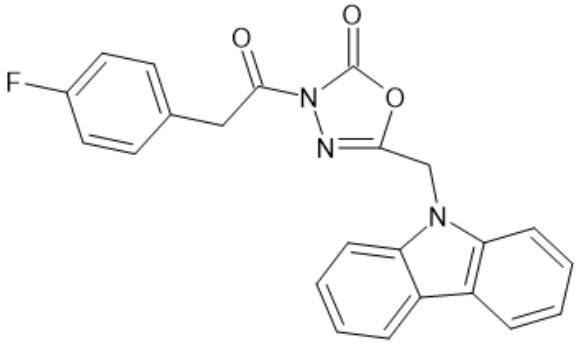


Compound 9

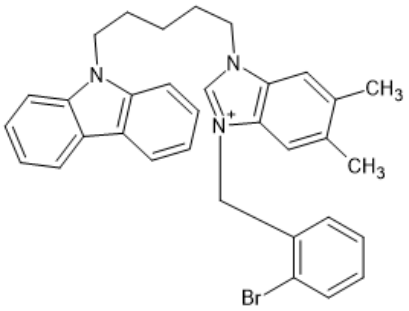
R_2=Cl



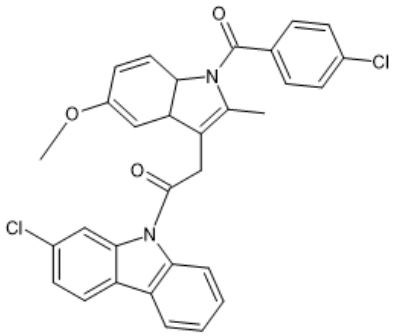
Compound 10



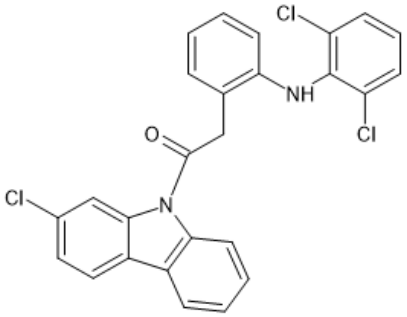
Compound 11



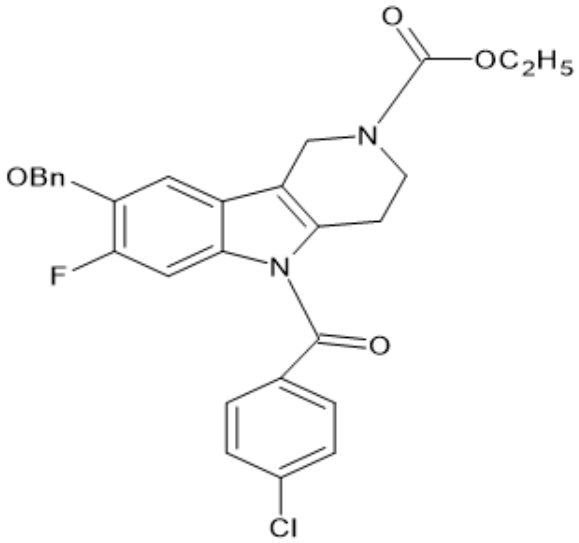
5,6 dimethyl benzimidazole substituted carbazole



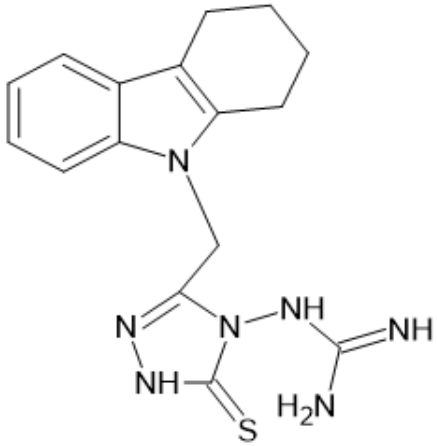
Compound CI



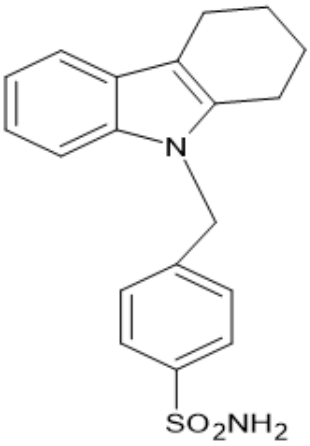
Compound CD



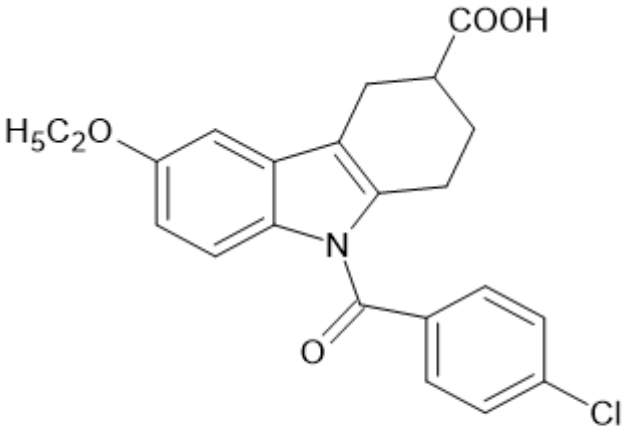
Compound 12b



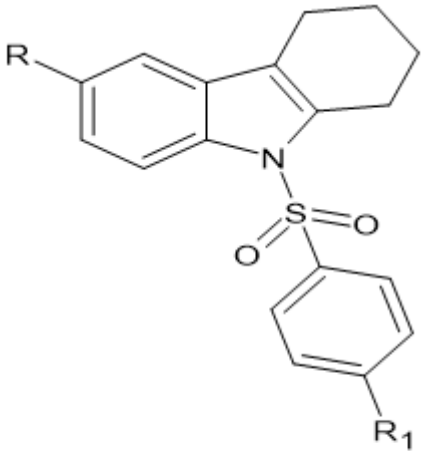
Compound TCZ-1b



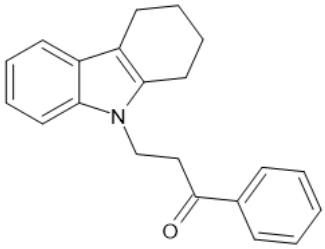
Compound TCZ-2a



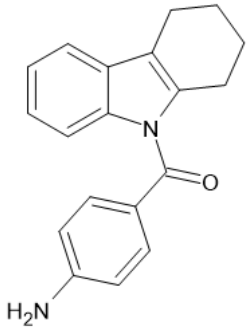
Compound 7a



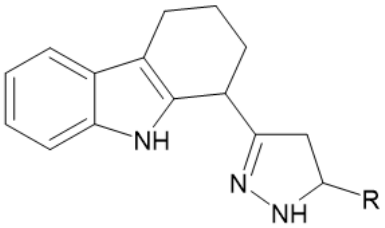
Substituted derivative



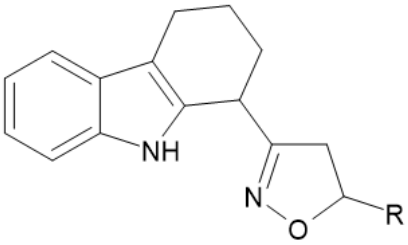
Compound J3



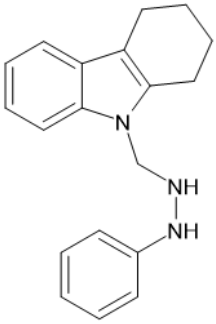
Substituted N-(4-amino benzoyl) 1,2,3,4- tetrahydro carbazole derivatives



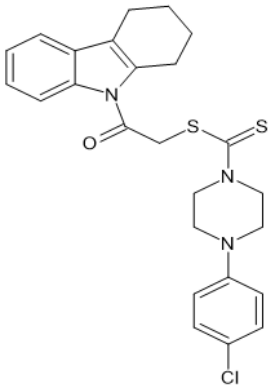
Chalconyl Isoxazolinyl tetrahydrocarbazole derivative



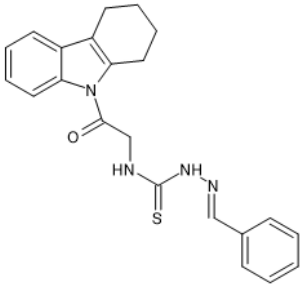
Pyrazolinyl 1,2,3,4 tetrahydrocarbazole derivatives



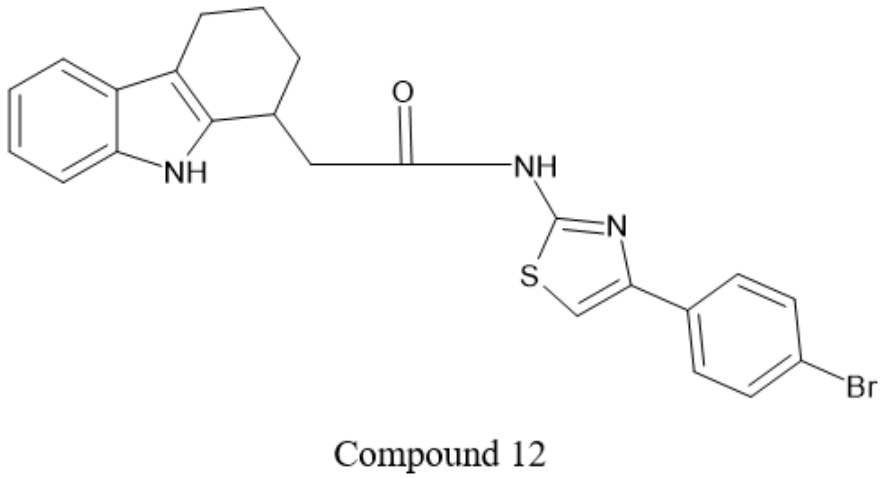
Compound PM1



Compound 6f



N- [2-oxo- 2-(1,2,3,4-tetrahydro-9H-carbazol-9-yl) ethyl] thiosemicarbazone derivatives



Compound 12

Figure 3: Structures of Specific Compounds.

FUTURE DIRECTIONS

Although carbazoles and tetrahydro carbazoles exhibit promising therapeutic potential, several research gaps remain. Most studies are limited to *in vitro* evaluations, with insufficient *in vivo*, pharmacokinetic, and toxicological data to support clinical translation. Systematic structure-activity relationship and computational studies are needed to guide rational drug design. Additionally, mechanistic insights into molecular targets remain inadequate. Future research should focus on sustainable synthetic strategies, comprehensive biological validation, and multitarget approaches to fully exploit the therapeutic potential of these scaffolds.

CONCLUSION

In this review article, it covers the chemistry, SAR, synthetic methods and biological evaluation of various carbazole and tetrahydrocarbazole derivatives. Carbazoles and tetrahydro carbazoles represent a privileged class of heterocyclic scaffolds with significant therapeutic potential because of their varied pharmacological actions, such as antineoplastic, antimicrobial, antiviral, neuroprotective and inflammation inhibitory activity. Recent progress in synthetic techniques has facilitated the development of novel compounds with improved potency, selectivity, and pharmacokinetic profiles. Activity-structure correlation further highlights the potential of functional group alterations in enhancing biological activity. Overall, carbazoles and tetrahydro carbazoles remain valuable leads in medicinal chemistry, offering opportunities for the development of next-generation therapeutic agents.

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ABBREVIATIONS

SAR: Structure-activity relationship; **DNA:** Deoxyribonucleic acid; **HIV:** Human immunodeficiency virus; **NMR:** Nuclear Magnetic Resonance; **MS:** Mass Spectrometry; **HRMS:** High-Resolution Mass Spectrometry; **IC_{50}:** Half maximal inhibitory concentration; **D3R:** Dopamine D3 receptor; **D2:** Dopamine D2 receptor; **FST:** Forced swim test; **TST:** Tail suspension test; **XDH:** Xanthine dehydrogenase; **PPARG:** Peroxisome proliferator-activated receptor gamma; **BBB:** Blood-brain barrier; **p-TsOH:** para-Toluenesulfonic acid; **DDQ:** 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone; **NSAIDs:** Non-steroidal anti-inflammatory drugs; **TCZ:** Tetrahydrocarbazole; **FTIR:** Fourier Transform Infrared Spectroscopy; **AMPK:** AMP-activated protein kinase; **DMSO:** Dimethyl sulfoxide; **IR:** Infrared spectroscopy; **DMF:** Dimethylformamide; **SRB:** Sulforhodamine B; **MTT:** 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; **LEDs:** Light-emitting diodes; **o-DCB:** ortho-Dichlorobenzene; **MW:** Microwave irradiation; **SPSS:** Statistical Package for the Social Sciences; **GlcN-6-P:** Glucosamine-6-phosphate; **HepG2:** Human hepatocellular carcinoma cell line; **HeLa:** Henrietta Lacks cervical cancer cell line; **MCF7:** Michigan Cancer Foundation-7 breast cancer cell line; **THCZ:** Tetrahydrocarbazole; **HCT116:** Human colorectal carcinoma cell line; **A549:** Human lung adenocarcinoma cell line; **SMMC-7721:** Human hepatocellular carcinoma cell line; **SW480:** Human colorectal adenocarcinoma cell line; **HL-60:** Human promyelocytic leukemia cell line; **Caco-2:** Human colorectal adenocarcinoma cell line; **Vero:** African green monkey kidney epithelial cell line.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS CONTRIBUTION

All authors contributed equally to the conception, literature review, drafting and final approval of the manuscript.

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